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TITLE: Clinical Impact of Hepatitis C Infection in Military Active Duty Women

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CONTRACTING ORGANIZATION: Walter Reed Army Medical Center
Washington, DC 20307-5001

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13. ABSTRACT *(Maximum 200*

To determine the prevalence of HCV among women in the US military, 3 categories of subjects were studied: 464 healthy women, 396 women in outpatient clinics and 89 women hospitalized for a variety of diagnosis (not liver disease). HCV epidemiological risks were sought. Sera were tested for ALT and anti-HCV (ELISA, RIBA, Ortho Lab). HCV RNA and HCV genotype were determined (Inno-LIPA, Belgium). Data analysis showed a mean age of 31.5 yrs (18-55). Racial distribution was 59% White, 29% Black, 7% Hispanic, 2% Asian. Overall 2.7% had abnormal ALT, eight (1.7%) healthy and 18 (3.7%) ill women. Mean abnormal ALT: 90, range: 53-260. Eleven women (1.16%) had anti-HCV. HCV infection was 1.7% (8) for healthy women and 0.5% for outpatients and 1.1% for hospitalized women. Four of the 11 had abnormal ALT, 7/11 had detectable HCV RNA. HCV genotypes were type one and three. HCV risks were present only in two women (occupation and promiscuity). HCV infection only correlated with age, older women had a higher prevalence (3.1%), younger women HCV rate was 0.6%. HCV infection did not correlate with ethnic background, job assignment, military rank or serum ALT level. In conclusion, HCV infection is silently present in military women.

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Maria Sjogren

Maria H Sjogren, COL, MC 5 July 1996
Principal Investigator

INTRODUCTION

Chronic viral hepatitis is a major public health concern in the United States and the world. About 1% of blood donors and 1.4% of apparently healthy American individuals are infected with the hepatitis C virus (1). For the past five years we studied a military population referred to the Walter Reed Army Medical Center because of chronic hepatitis, the number of patients is slightly over 400. This patient population was characterized clinically and by serological markers as chronic hepatitis B and chronic hepatitis C. These subjects have participated in three major epidemiological studies (2,3,4) and in two therapeutic trials which are ongoing (5,6). Our patients are young with a mean age of 41 years (range 18-76 years old); the risk of infection with hepatitis viruses is largely unknown. Sexual transmission accounts for 8% of the infections (2,3). Most patients (95%) have detectable levels of viral replication markers (HBV DNA or HCV RNA, respectively). When liver biopsies are evaluated, 98% of patients have the diagnosis of chronic hepatitis. Many of these populations have reduced working hours because of associated symptomatology. About 2% have developed hepatocellular carcinoma. Approximately 50% of the patients with chronic viral hepatitis participated in therapeutic trials. Efficacy of the medications varied according to the therapeutic regimen and ranged between 10% and 40% for chronic hepatitis C and approximately 40% response for chronic hepatitis B (unpublished data). Preliminary study on the hepatitis C virus genotype shows a variety of genotypes (1a, 1b, 3a and possibly 7,8 and 9). This range of genotypes is likely due to the worldwide deployment of US military service members.

A gap in the knowledge regarding the prevalence of hepatitis C infection among military women was identified. As a result, the Department of Defense Women's Health Research Program funded a study where about 1,000 active duty women were tested for serological markers of hepatitis C. The analysis of this work is discussed in this manuscript.

BODY

Study Group

The study group included a total of 949 active duty females. Among them, 464 were healthy women and 485 women consulted a physician or were hospitalized for a variety of medical reasons which did not include liver disease. Demographic data and epidemiological risks of HCV infection were sought with the aid of a questionnaire.

	"n"
• Group A: Healthy women	464
• Group B: Clinic visits (not liver related)	396
• Group C: Hospitalized (not liver related	89
Total	949

Serological assays

A serum specimen was collected from each subject. Sera were tested for makers of liver disease (alanine aminotransferase: ALT) and markers of HCV infection (antibody to HCV: anti-HCV).

- Anti-HCV was detected by ELISA 2.0 (Ortho Laboratories, Piscataway, NJ) and by RIBA-II (recombinant immunoblot assay) (Ortho Laboratories, Piscataway, NJ)

- In addition, sera with detectable anti-HCV, was further studied for the presence of viral RNA (HCV RNA) by qualitative and quantitative assays:
  - RT PCR (primers 5' UTR)
  - bDNA (Chiron Laboratories, Emeryville, CA)
  - Amplicor (Roche Laboratories, New Jersey)

- HCV genotype was assayed if HCV RNA was present in serum.
  - Inno-LIPA assay, Innogenetics Laboratories, Belgium

Questionnaire

The following information was obtained

- Demographics
  Age (years)
  Race

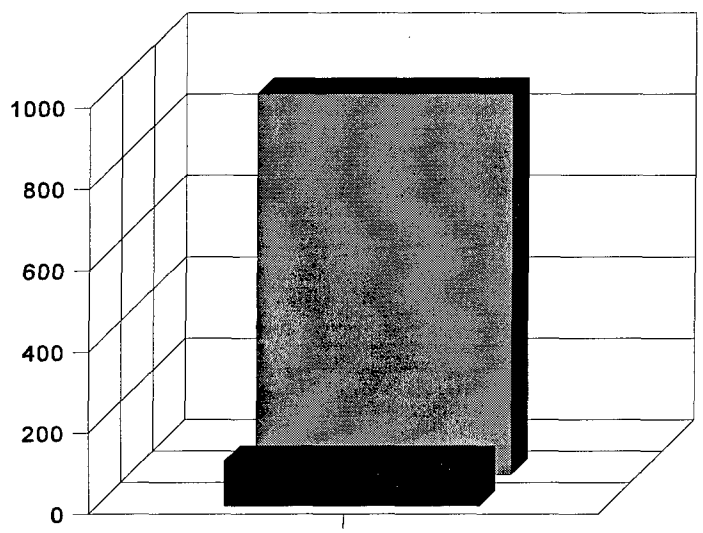
Military rank (officer or enlisted)
Job assignment (health care or office work)

- Risk Factors
  Received blood products
  History of intravenous drug abuse
  History of liver disease
  Sexual activity with known HCV-infected partners
  Promiscuity (more than one sexual partner at a time)

Data Analysis

Data were analyzed for prevalence rates in each of the study groups. Overall prevalence of HCV in military active duty women was calculated.
Correlations between HCV infection and age, military rank, occupation, risk factors and serum ALT levels were done.

RESULTS



Of the 949 women, 11 (1.16%) tested positive for anti-HCV. Their demographic data and hepatitis C markers, HCV RNA and HCV genotype are depicted in Table 1. Of these 11, 4 had abnormal serum ALT levels ranging between 62 and 110 u/L.

Group A: HCV rate of 1.7% (8/ 464) and abnormal ALT rate of 1.7% (8/ 464).
Group B: HCV rate of 0.5% (2/396) and abnormal ALT rate of 2.8% (11/ 396).
Group C: HCV rate of 1.1% (1/ 89) and abnormal ALT rate of 7.9% (7/89).

TABLE 1

Serological Profile on the Eleven HCV-Infected Subjects

Patient	Age/Race	ALT * u/L	ELISA OD	RIBA II	HCV RNA (RT-PCR)	Genotype **
1	38/Black	24	2.5 (+)	Positive	Positive	1a
2	48/White	14	0.64 (+)	Negative	Negative	ND
3	35/White	26	2.5 (+)	Positive	Negative	ND
4	32/Black	39	1.27 (+)	Negative	Positive	1a,3
5	24/Hispanic	33	0.72 (+)	Negative	Positive	3
6	42/Unknown	18	1.04 (+)	Indeterm.	Negative	ND
7	28/White	110 ↑	2.5 (+)	Positive	Positive	1a
8	45/White	68 ↑	2.5 (+)	Positive	Positive	1b
9	27/White	62 ↑	2.5 (+)	Positive	Positive	1a
10	46/White	68 ↑	2.5 (+)	Positive	Positive	1a
11	43/Hispanic	37	2.5 (+)	Positive	Negative	ND

* ALT normal level: 9-52

** ND: HCV genotype cannot be done when HCV RNA is undetectable

TABLE 2

Comparison of Three Methods to Detect HCV RNA

Patient	HCV RNA (RT-PCR)	HCV RNA (CHIRON) bDNA Eq/mL x 10^5	HCV RNA (ROCHE) Amplicor Copies/mL
1	Positive	27.11 (Positive)	340,135 (Positive)
2	Negative	< 3.5 (Negative)	(Negative)
3	Negative	< 3.5 (Negative)	(Negative)
4	Positive	< 3.5 (Negative)	(Negative)
5	Positive	< 3.5 (Negative)	(Negative)
6	Negative	< 3.5 (Negative)	(Negative)
7	Positive	15.9 (Positive)	134,161 (Positive)
8	Positive	196.2 (Positive)	458,900 (Positive)
9	Positive	8.6 (Positive)	81,760 (Positive)
10	Positive	14.1 (Positive)	105,600 (Positive)
11	Negative	< 3.5 (Negative)	(Negative)

Table 2 shows the comparison of three methods to detect HCV RNA. Our results are in agreement with the published literature, where the qualitative RT-PCR test is the most sensitive for detection of HCV RNA. The Chiron test and the Amplicor have the advantage of measuring titer of RNA in serum, however the sensitivity is low.

TABLE 3

Comparison of the Sensitivity of HCV RNA by RT-PCR, bDNA and Amplicor

	RIBA +	RIBA -	bDNA +	bDNA -	Amplicor +	Amplicor -
HCVRNA +	5	2	5	2	5	2
HCVRNA -	2	2	0	4	0	4
Amplicor +	5	0	5	0		
Amplicor -	2	4	0	6		
bDNA +	5	0				
bDNA -	2	4				

Of the 11 subjects that were Elisa positive, 7 were Riba positive, 7 were HCV RNA positive, 5 were bDNA positive and 5 were Amplicor positive.

Correlation of HCV infection and Demographics or Risk Factors

HCV infection correlated with age. Among young adults (age 18 - 30) the infection rate was 0.6% (3/487). While among adults aged 31 to 45 years, the infection rate was 1.5% (6 /396). In contrast, older adults (age > 45 years) the infection rate was 3.1% (2/64). HCV infection varied slightly among races. Caucasians had a 1.1% infection rate (6/543). African Americans had a 0.7% infection rate (2/ 287). Hispanics had a 3.9% infection rate (2/51). There were no Asian subjects with HCV (0/30).

Among the risk factors, HCV infection correlated with history of prior liver disease (other than viral hepatitis) and receipt of blood products. Anti-HCV was detectable in 10.5% of subjects who had prior liver disease (2/19) and in 2.9% (2/69) of subjects who had received blood products. HCV infection did not correlate with serum ALT (Figure 2), health status, military rank (Figure 3), or type of work. Overall the abnormal ALT rate was 2.7% (26/949)

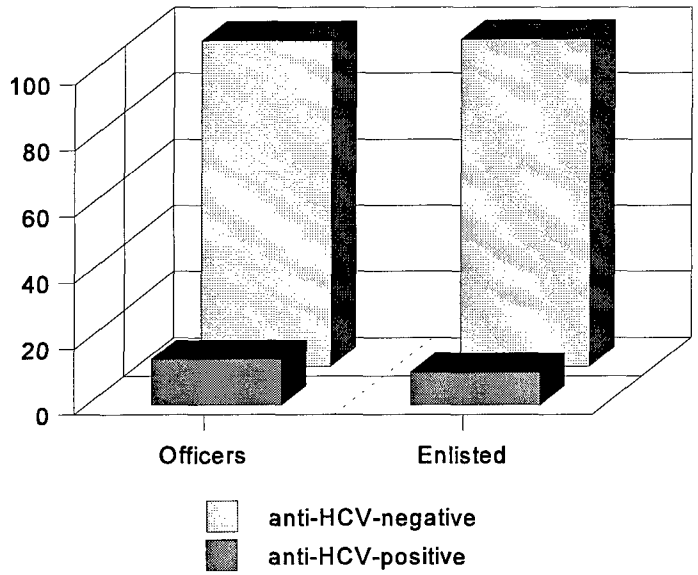


Figure 2. Shows the lack of correlation between abnormal ALT and HCV infection.

Abnormal ALT
Group A: 1.7% (8/ 464)
Group B: 2.8% (11/396)
Group C: 7.9% (7/89).

Abnormal ALT did correlate with other risk factors (liver disease, blood products, and promiscuity) and health status. 7.1% of subjects who received blood products had abnormal serum ALT levels (5/70). 15.8% of subjects who have liver disease had abnormal ALTs (3/19). 4.2% of subjects who had more than one sexual partner the previous year had an abnormal serum ALT value. Abnormal ALT varied slightly among races as well. The rate of ALT abnormality was 2.9% among Caucasians (16/543), 2.4% among African Americans (7/ 289), 2% among Hispanics (1/51) and, 6.7% among Asians (2/30).

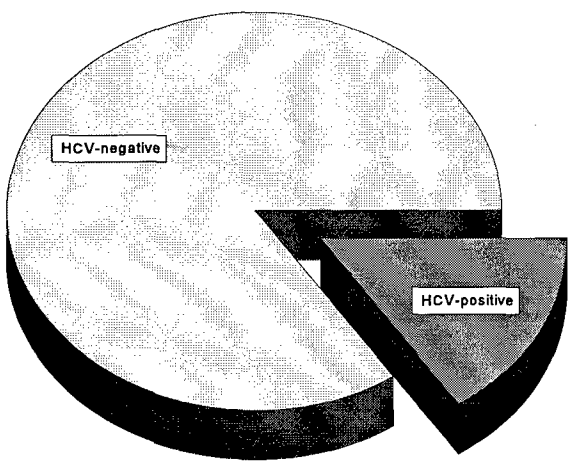


Figure 3. Depicts the same proportion of anti-HCV among officers (1.4%) and enlisted(1%)military women (p= .52)

The anti-HCV optical density of the Ortho assay was higher in patients with detectable HCV RNA (RT-PCR) than in patients with undetectable HCV RNA (Table 2). Quantitative HCV RNA tests were insensitive but provided titer of the viral RNA when positive.

CONCLUSIONS

Hepatitis C infection is detectable in military women at similar rates as reported in the civilian population. However, this infection appears to be silent. The HCV genotypes observed were type 1 and 3, which are known to associate with progressive liver disease. These women are at risk of significant liver disease. Clinical monitoring of these subjects is in order. Since the start of this study, a new hepatitis virus has been discovered, the hepatitis G (HGV) (6). It is known to associate to HCV infection. It would be of importance to test this serum collection for HGV. Similarly, a study of service men in the same categories as the studied women needs to be carried out.

BIBLIOGRAPHY

1. Gastroenterology Clinics of North America 1994;23:437-455
2. Proceedings of International Symposium on Viral hepatitis and Liver Disease, Tokyo, Japan, 1994: 450-454
3. Gastroenterology 1994;106:A998
4. Gastroenterology 1996;110:A1330
5. Hepatology 1994;20:2007A
6. Science 1996;271:505-508
6. Walter Reed Army Medical Center, Clinical Trial WU# 9296

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
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REPLY TO
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